Original Article

The clinical value of ^{18}F-fluoroestradiol in assisting individualized treatment decision in dual primary malignancies

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Background: For patients with previously diagnosed dual primary tumors, it is usually difficult to determine the diagnosis and treatment of stage IV recurrence. The study was to explore the influences of ^{18}F-fluoroestradiol positron emission tomography/computed tomography (^{18}F-FES PET/CT) in the diagnosis of estrogen receptor (ER) positive breast cancer combined with other primary tumor with distant metastases.

Methods: Multidisciplinary team were organized to explore the definite clinical value of ^{18}F-FES PET/CT in stage IV patients suffered from ER-positive breast cancer and another primary tumor synchronously or metachronously. Thirty-two female patients were retrospectively analyzed who underwent ^{18}F-FES PET/CT scans in our center. Before and after reading ^{18}F-FES reports, the team members from department of surgery, oncology and radiotherapy should make decisions of management strategy.

Results: Totally, the multidisciplinary team completed the management decision-making of the 32 patients before and after ^{18}F-FES PET/CT scans. 87.5% (n=28) of the patients were considered to benefit from ^{18}F-FES reports for diagnosis and treatment decisions. Out of the 28 patients, 7 patients (7/32, 21.9%) were considered to definitely change the management strategies while 12 patients (12/32, 37.5%) was instructive to develop management plans after the scan. The other 9 patients were suggested reassuring decision-making process by ^{18}F-FES PET/CT.

Conclusions: ^{18}F-FES PET/CT scans have clinical effects on diagnosis and treatment strategies of stage IV patients suffered from ER-positive breast cancer and another primary tumor.

Keywords: ^{18}F-fluoroestradiol positron emission tomography/computed tomography (^{18}F-FES PET/CT); double primary cancer; estrogen receptor-positive breast cancer (ER-positive breast cancer); management strategy

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Introduction

WHO Global Cancer Observatory 2018 registry suggested that 2.09 million breast cancer cases have been diagnosed newly, being the second most frequent tumors worldwide (1). According to cancer statistics from China in 2015, breast cancer was estimated to account for 15% of newly diagnosed cancers (2). With advances in cancer early detection and management, the survival of patients has improved. An increasing number of patients, however, acquire multiple primary cancers for various reasons, such as environmental modifications, genetic predisposition, therapy, increased surveillance, or prolonged survival (3). A cohort of 2,116,163 patients was identified in a study, 170,865 of whom (8.1%) developed a second primary malignancy, and more than 50% of the patients with 2 incident cancers died of their secondary malignancy (4). Another study showed that 17.0% (14,952/87,752) of breast cancer patients developed second primary cancer after a median follow-up of 5 years (5). Due to the complicated and changeable diagnosis and treatment of multiple primary tumors, there is no unified diagnosis and treatment standard at present. The risk of secondary primary cancer following breast irradiation has been reported to be higher than that of the normal population, so the status of late effects associated with treatment needs to be assessed to reduce this risk (6). Several studies documented that patients with MGUS have a higher risk of myeloid malignancies and patients with MM have an increased risk of developing AML, acute lymphoblastic leukemia, and some solid tumors. Moreover, WM patients appear to be at increased risk for AML, diffuse large B-cell lymphoma, thyroid cancer, and melanoma (7). It has been reported that the presence of multiple malignancies is a significant adverse prognostic factor for lung cancer, and short treatment intervals are also associated with poor prognosis (8). Studies have reported a 7% risk of multiple primary malignancies in patients with phacomatoses (9). Actually, there was no standard treatment or procedure under most of the patients with dual primary malignancies, especially for recurrent cancer. Therefore, it is important to detect differences in the clinical, pathological, and treatment characteristics among patients with multiple primary cancers.

Clinical indicators, pathology and medical imaging are the basis of the diagnosis and staging of various cancers (10). Specifically, molecular imaging has more abundant information than morphological imaging to assist physicians to make accurate clinical diagnosis. The previous study shows that positron emission tomography/computed tomography (PET/CT) is more sensitive and specific in the staging of many cancers compared with other imaging methods (11). Endocrine therapy is an important option in management strategy of breast cancers because 70–80% of them are estrogen receptor (ER)-positive and/or progesterone receptor-positive (12). The ER expression in breast cancer plays a key role in prognosis and the treatment strategy decision (13). ^{18}F-fluoroestradiol (^{18}F-FES) has been recognized to observe and quantify ER expression *in vivo* as a non-invasive and molecular imaging technique (14,15). Previous studies suggested that the uptake situation of ^{18}F-FES in lesions were highly corresponded to the ER expression level of immunohistochemical (IHC) staining on tumor biopsies (16,17).

Previous studies demonstrated that ^{18}F-FES PET/CT is used to predict the effect of endocrine therapy in advanced or metastatic ER-positive breast cancer patients and to reveal the heterogeneity of multiple lesions (18-20). The clinical impact of ^{18}F-FES in patients who suffered from ER-positive breast cancer and another primary cancer was rarely studied, though the application of ^{18}F-FES in metastatic breast cancer has been extensive (18,19). This study was to investigate the value of ^{18}F-FES on lesion detection and individual management plans in stage IV patients suffered from ER-positive breast cancer and another primary cancer synchronously or metachronously.

Methods

Patients collections

In our study, 32 patients who suffered from ER-positive breast cancer and another primary cancer synchronously or metachronously were screened from our workstation between July 2017 and July 2020 in the center. All patients who met the following criteria were enrolled: (I) immunohistochemically confirmed ER-positive breast cancer; (II) diagnosed with another primary cancer by pathology; (III) had metastasizing lesions confirmed by pathological processes or imaging; (IV) underwent ^{18}F-FES PET/CT after being diagnosed with dual primary cancer. Significantly, the following exclusion criteria had been implemented: (I) patients diagnosed purely dual ER+ breast cancers were excluded; (II) some of the second ER+ non-breast cancer like ovarian cancer should be ruled out, because it may make the additional value on decision making in this case limited. The criteria for diagnosing

multiple primary tumors were as follows (3,21): (I) simultaneity or heterochrony is not one of the diagnostic criteria. (II) A primary cancer is defined as originating from the primary tumor or tissue, rather than a recurrence or metastasis. (III) An organ or tissues is defined in accordance with *the ICD-0 Third Edition* standard, where one or a pair of organs or tissues can produce only one type of cancer of the same morphology. (IV) Even if tumors diagnosed at the same site have different morphologies (following ICD-O morphology code), they should be considered as multiple primary malignancies. We reviewed 61 patients suffered from dual primary cancer in total and finally enrolled 32 patients for this study. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethical standards of the institutional research committee. The requirement of informed consent was not necessary because of the retrospective nature of this study.

The multidisciplinary team provided treatment plans referring the full medical histories of 32 patients before ^{18}F-FES PET/CT scan, and then denoted the intended management improvements after reading ^{18}F-FES information. All the physicians who took part in the multidisciplinary team in our study were attending doctors and above from surgery department, medical oncology, and department of radiotherapy. When the team members had different opinions on the diagnosis and treatment of a certain patient, the whole group will discuss and vote. And a finial decision will be adopted when more than 3/5 physicians agree. They had not been informed about any medical history of the selected patients before. A change was defined as a definite difference in management strategy before and after ^{18}F-FES PET/CT scan. Specifically, a change of treatment strategy was adopted when over 2/3 of physicians provided the same decision-making before and after the ^{18}F-FES PET/CT.

Synthesis of ^{18}F-FES and quality control

The preparation and modification of ^{18}F-FES was referred to published methods (22) and previous studies (23). The MMSE precursor and the authentic ^{18}F-FES were purchased from licensed companies. The total preparation time was approximately 100 min, and the corrected radiochemical yield was approximately 40% at the end of synthesis. The ^{18}F-FES radiochemical purity was greater than 99%.

PET/CT imaging

For ^{18}F-FES PET/CT imaging, all patients required a washout period of the ER antagonist (24). Each patient was given about 222 MBq (6 mCi) of ^{18}F-FES intravenously for 1 to 2 minutes. For data acquisition, ^{18}F-FES PET/CT scans were performed using a combined PET/CT scanner (Siemens Medical Systems, Biograph 16 HR or mCT flow PET/CT scanner) started approximately 1 h after the injection. They will be scanned from the top of their head to the base of their thighs with 2 minutes per bed position.

Image interpretation

Lesions identified via ^{18}F-FES PET were corroborated by CT and/or other imaging. For quantitative analysis, ^{18}F-FES accumulation was assessed on a workstation by two experienced nuclear medicine physicians by calculating the standardized uptake value (SUV) in the regions of interest placed over the suspected lesions. both of two physicians are experienced nuclear medicine clinicians with the title of attending or above, and they are mainly engaged in the research of breast cancer. SUV was calculated in pixels as radioactivity/(injected dose/body weight). The value of SUVmax was automatically measured by the analysis software for each lesion. The margin threshold of ^{18}F-FES was set at 1.8 according to a previous study (23). Except bone metastatic lesions, the number of target lesions for each patient on imaging were recorded. The actual number was also counted when bone metastases had 10 or less than 10 lesions. As for the uncountable and widespread bone metastases, an arbitration count of up to 10 lesions of the largest ^{18}F-FES PET intensity lesions were taken for the calculation.

Statistical analysis

The number of ^{18}F-FES-positive lesions was calculated as the total number, and lesions were excluded if they were negative. Due to the high physiological uptake of ^{18}F-FES in liver tissues, liver lesions were excluded from the analyses.

Results

Patient population

We reviewed 61 patients diagnosed with dual primary

cancer in total and finally enrolled 32 patients for this study. The data of 32 female patients diagnosed synchronously or metachronously with ER-positive breast cancer and another primary tumor who underwent ^{18}F-FES PET/CT in our center were collected in our study. Seven patients were diagnosed with double primary breast cancer (one with ER+ and the other one with ER–), while the other 25 patients were diagnosed with another primary cancer except breast cancer. The details of the patient data are summarized in *Tables 1*,*2*.

^{18}F-FES PET/CT imaging data analysis

Among the 32 patients in our study, we found 495 total lesions. Patients were divided into three groups according to ^{18}F-FES uptake patterns: (I) FES+ group (n=18): all metastatic lesions were ^{18}F-FES avid (316 lesions). (II) FES+/– heterogeneity group (n=4): ^{18}F-FES avid (36 lesions) and absent (39 lesions) lesions coexisted in one patient. (III) FES– group (n=10): all metastatic lesions were ^{18}F-FES absent (104 lesions).

Referring treatment suggestions from the multidisciplinary team

The physicians in the multidisciplinary team provided the treatment strategy of 32 patients diagnosed with ER-positive breast cancer combined with another primary tumor before and after ^{18}F-FES PET/CT scan. *Table 1* summarized the impact of ^{18}F-FES PET/CT on the intended management. Referring to the considerations from the multidisciplinary team, results were divided into the following four categories: (I) change: the management strategies of patients were definitely changed by ^{18}F-FES PET/CT scan; (II) instruction: no treatment recommendations were provided before the scan and a proposal of treatment were presented after; (III) reassurance: the physicians recommended the same management strategy before and after ^{18}F-FES PET/CT and they considered the FES reports could reassured outcomes of knowledge, understanding and confidence in treatment decision; (IV) no reference value: the multidisciplinary team considered that ^{18}F-FES PET/CT has no application value mentioned above. Most patients (28/32, 87.5%) were considered that ^{18}F-FES PET/CT scan played a valuable role in the decision-making of the treatment strategy.

Detailed changes in the diagnosis and management after ^{18}F-FES PET scanning were summarized in *Table 1*. Among the 32 patients diagnosed with ER+ breast cancer and another primary tumor, 28 patients (87.5%), including 15 patients of FES+ group, 4 of FES+/– heterogeneity group and 9 FES- group members, were considered to achieve reference value in management strategy by ^{18}F-FES PET/CT scan. Out of the 28 patients, 7 patients (3 FES+ group members, 2 FES+/– heterogeneity group patient, and 2 FES– group members) were considered to definitely change the managements by the scan. 12 patients (7 FES+ group members, 2 FES+/– heterogeneity group members, and 3 FES– group members) had not been offered a proposal of treatment strategy before ^{18}F-FES PET/CT scan. As for the other 9 patients (5 FES+ group members and 4 FES– group members), the multidisciplinary team considered for the same treatment strategy before and after the ^{18}F-FES PET/CT scan, but the physicians still regarded the scan as having an assistant role in both diagnosis and management. The FES results could increase outcomes of understanding and confidence in the decision-making process.

At the level of management decision, for 7 patients who were considered changing the treatment strategy definitely by ^{18}F-FES PET/CT scan, the details were as follows: (I) the multidisciplinary team considered to change chemotherapy to endocrine therapy for 3 FES+ group patients; (II) 1 FES+/– heterogeneity group member was changed symptomatic treatment to endocrine therapy, and another patient was changed endocrine therapy to chemotherapy; (II) 2 FES– group members were suggested changing endocrine therapy to chemotherapy. Among the 12 patients whose management strategy could not be confirmed before the ^{18}F-FES PET/CT scan, all of the patients in FES+ group (n=7) were recommended for endocrine therapy, 2 of which were for combined targeted therapy after referring to the ^{18}F-FES PET/CT reports. And endocrine therapies were suggested in both the 2 patients in FES+/– heterogeneity group. As for 3 patients in FES– group, chemotherapies were recommended for them after the scan, and one of which was for combined targeted therapy.

Additionally, out of the 9 patients (5 FES+ group members and 4 FES– group members), the multidisciplinary team adhered to the notion that the scan played an instructive role in both diagnosis and treatment although it could not change management strategy: (I) 2 FES+ group patients were considered to treat with endocrine therapy alone and the other 3 in the same group were recommended for a combination of endocrine and targeted therapy; (II) chemotherapies were recommended in 3 FES– group

Table 1 Decision-making of managements by ^{18}F-FES PET/CT scan based on the study population (n=32)

No.	Age	Primary tumors	ER+ BC	The amounts of FES–	The amounts of FES+	Location of FES+ lesions	^{18}F-FES PET/CT value	Therapy before scan	Therapy after scan
1	52	DBC	L	3	0	0	III	CHEMO	CHEMO
2	42	DBC	R	15	24	LNs, MB	I	BSC	ET
3	41	DBC	R	16	0	0	III	CHEMO	CHEMO
4	50	DBC	R	10	0	0	I	ET	CHEMO
5	72	LBC, EC	L	6	5	MLNs, HLNs, pleura	II	–	ET
6	44	DBC	L	1	0	0	IV	–	–
7	37	DBC	R	0	13	ALNs, IMLNs, SLNs, MLNs, MB	I	CHEMO	ET and TT
8	59	LBC, CC	L	0	18	MLNs, MB	III	ET	ET
9	65	RBC, LC	R	8	0	0	I	ET	IT
10	88	DBC	R	0	22	LNs, MB, SNs	I	CHEMO	ET
11	63	DBC, LC	D	0	6	SLNs, MLNs, RLNs, lung, pleura	II	–	ET
12	65	RBC, TC	R	0	28	CTLNs, MB	II	–	ET
13	42	RBC, LC	R	9	4	ALNs	II	–	ET
14	68	DBC, CRC	L	15	0	0	III	CHEMO	CHEMO
15	69	RBC, LC	R	0	15	MLNs, MB	II	–	ET and TT
16	55	RBC, RC	R	0	26	MLNs, HLNs, MB	II	–	ET
17	69	LBC, LC	L	1	0	0	II	–	TT
18	34	LBC, TC	L	0	3	IMLN, MLN, MB	IV	ET	ET
19	71	LBC, TC	L	0	5	ALNs, IMLNs, SN	III	ET	ET
20	61	LBC, RC	L	0	17	MLNs, HLNs, MB, pleura	II	–	ET
21	71	LBC, HL	L	0	21	Lung, MB	IV	ET and TT	ET and TT
22	62	LBC, GC	L	27	0	0	II	–	CHEMO and TT
23	57	LBC, LC	L	0	23	MLNs, HLNs, MB	IV	ET	ET
24	51	LBC, LC	L	0	10	MB	III	ET and TT	ET and TT
25	66	LBC, PNEN	L	0	12	ALNs, MB	II	–	ET
26	62	RBC, CRC	R	0	28	LNs, MB, lung	III	ET	ET
27	68	RBC, LMS	R	17	0	0	II	–	TT
28	63	DBC, LC	D	0	21	LNs, MB	II	–	ET
29	40	LBC, TC	L	6	0	0	III	ET	ET
30	62	LBC, CRC	L	9	3	ALNs	I	ET	CHEMO
31	32	DBC, GC	D	0	32	LNs, MB, pleura, peritoneum, ovaries, muscle	I	CHEMO	ET and TT
32	57	RBC, MALT	R	0	16	CTLN, MB	III	ET and TT	ET and TT

I: changes in management strategy; II: instructive in management strategy; III: reassurance in management strategy; IV: no reference value in management strategy. ^{18}F-FES, ^{18}F-fluoroestradiol; PET, positron emission tomography; CT, computed tomography; ER, estrogen receptor; ER+, ER positive; FES+, ^{18}F-FES positive; BC, breast cancer; DBC, double breast cancer; LBC, left breast cancer; CRC, colorectal cancer; EC, endometrial cancer; CC, cervical cancer; LC, lung cancer; GC, gastric cancer; RC, renal carcinoma; TC, thyroid cancer; HL, Hodgkin's lymphoma; PNEN, pancreatic neuroendocrine; LMS, leiomyosarcoma; RBC, right breast cancer; MALT, mucosa-associated lymphoid tissue; ALN, axillary lymph node; BSC, best support care; CHEMO, chemotherapy; CTLN, cervicothoracic lymph nodes; ET, endocrine therapy; HLN, Hilar lymph nodes, IMLN, internal mammary lymph node; IT, immunotherapy; LN, lymph node; MB, multiple bones; MLN, mediastinal lymph node; RLN, retroperitoneal lymph nodes; SLN, supraclavicular lymph node; SN, subcutaneous nodules; TT, targeted therapy; –, no proposal.

Table 2 The specific situation of the multipal cancer (n=32)

No.	Age	The date of ER+ BC	The date of another tumor	Histopathology of another tumor	Another tumor size (cm)
1	52	2004.11	2016.03	ER– infiltrating ductal	2.5×1.4
2	42	2016.6	2013.04	ER– infiltrating ductal	2.7×1.8
3	41	2018.10	1995.05	ER– infiltrating ductal	1.9×1.7
4	50	2017.12	2004.12	ER– infiltrating ductal	1.5×1.3
5	72	2007.06	2016.05	Endometrial adenocarcinoma	–
6	44	2011.05	2013.09	ER– infiltrating ductal	2.6×2.1
7	37	2009.05	2012.11	ER– infiltrating ductal	1.2×1.1
8	59	2007.04	2013.04	Cervical squamous carcinoma	1.1×0.6
9	65	2017.04	2017.05	ER– pulmonary squamous carcinoma	2.3×1.8
10	88	1998.12	1997.06	ER– infiltrating ductal	3.7×2.6
11	63	2002.07, 2016.11	2015.03	ER– pulmonary adenocarcinoma	1.4×1.4
12	65	2006.06	2015.05	Thyroid papillary carcinoma	2.1×1.6
13	42	2018.03	2018.03	ER– pulmonary adenocarcinoma	2.0×1.8
14	68	2019.12	2012.08, 2019.12	Colonic mucinous carcinomas, ER– infiltrating ductal	–, 2.8×2.4
15	69	2011.09	2011.09	Pulmonary adenocarcinoma	3.9×2.1
16	55	2017.08	2018.10, 2019.02	Clear cell renal cell carcinoma, rectal NET	–, 0.6
17	69	2019.08	2017.11	Pulmonary adenocarcinoma	2.3×1.8
18	34	2015.05	2018.10	Thyroid papillary carcinoma	1.6×0.9
19	71	1994.03	2006.11	Thyroid papillary carcinoma	–
20	61	2009.01	2014.05	Clear cell renal cell carcinoma	2.1×1.9
21	71	2007.04	2011.08	Hodgkin's lymphoma	–
22	62	2009.11	2017.03	Gastric adenocarcinoma	–
23	57	2009.03	2014.07	Pulmonary adenocarcinoma	0.7×0.5
24	51	2016.09	2020.01	Pulmonary adenocarcinoma	1.3×0.9
25	66	2018.08	2019.03	Pancreatic NET	9.6×7.6
26	62	2014.06	2006.08	Colonic adenocarcinoma	–
27	68	2019.11	2018.11	Uterine leiomyosarcoma	5.3×4.8
28	63	2019.07	2017.07	Pulmonary adenocarcinoma	1.3×1.1
29	40	2017.09	2003.03	Thyroid papillary carcinoma	–
30	62	2019.12	2015.01	Colonic mucinous carcinoma	–
31	32	2017.09, 2018.10	2016.01	Gastric adenocarcinoma	–
32	57	2006.06	2020.06	Non-Hodgkin lymphoma	–

"–" indicates that data is not available for various objective reasons. ER, estrogen receptor; ER+, ER positive; BC, breast cancer; NET, neuroendocrine tumor.

patients while the last patient were considered to maintain current endocrine therapy.

Discussion

To our knowledge, this is the first explorative study conducted to systematically evaluate the clinical value of ^{18}F-FES PET/CT in the implemented management of diagnosed double primary tumor patients. Previous studies have successfully demonstrated that ^{18}F-FES PET/CT is a sensitive method for monitoring regional estrogen binding in advanced and metastatic ER-positive breast cancer (25) and validated that ^{18}F-FES uptake quantitation correlates well with ER expression measured by IHC (15,17,26). The objective data further confirmed that FES can be helpful for patients to avoid ineffective or excessive management (25,27). Some lesions of ER-positive characteristics were converted to ER-negative phenotypes after treatment, and the heterogeneity of ^{18}F-FES uptake was higher in patients with recurrent or metastatic breast cancer than untreated patients (23,28). Meanwhile, FES-PET heterogeneity may potentially identify the subset of ER positive, metastatic breast cancer patients who benefit from individualized treatment programs. Above all, ^{18}F-FES PET/CT could provide an amount of information for physicians to perfect diagnosis and management strategy.

Our results showed for the first time that ^{18}F-FES PET/CT could impact the management of diagnosed ER+ breast cancer combined with another primary cancer. In the current study, ^{18}F-FES PET/CT was instructive to improve the treatment strategy in 87.5% of patients (28/32). These results may probably mainly arise from several aspects as follow: (I) the ^{18}F-FES PET/CT reports confer potentially impact on future diagnosis and treatment decision. (II) FES– group patients have diagnostic values in excluding metastasis deriving from breast cancer. (III) The results could increase outcomes of knowledge, understanding, and confidence in the decision-making process. Out of 28 patients, ^{18}F-FES PET/CT definitely changed the diagnosis and treatment strategy in 7 patients, including 3 patients in FES+ group, 2 patients in FES+/– heterogeneity group, and 2 patients in FES– group, which is an optimistic probability of changing treatment decisions. These changes in therapeutic strategy potential to may be crucial to the prognosis of the patients.

For the patients in FES– group, the exclusion of deriving from breast cancer should be considered when the possibilities as follows were excluded: (I) metastases of ER-positive characteristics were converted to ER-negative phenotypes after previous treatment; (II) all of the lesions didn't show ^{18}F-FES uptake due to false negativity; and (III) not all metastases derived from the same primary cancer. Meanwhile, we should be aware that the second possibility was almost based on the situation that all of metastases were small and they showed FES-negative synchronously due to false negatives. Therefore, the probability of such a situation is very low. And the third has an extremely low possibility because of the principle of monism. Nevertheless, it is almost certain that the FES– group patients weren't sensitive to endocrine therapy alone. The above view was also supported by the results that none of the selected group members except a special case were considered by physicians to received endocrine therapy alone. This particular FES– group patient was diagnosed thyroid cancer in 2000 and ER+ breast cancer in 2017. It is worth mentioning that she was detected pulmonary metastasis from thyroid cancer by pathological test in 2003. The patient was followed up until 2017, when breast cancer was diagnosis. ^{18}F-FES PET/CT result showed that there was no metastasis other than lung FES-negative metastasis. Based on the above medical history, physicians' preference for pulmonary metastasis is thyroid cancer, and follow-up can be continued. ER+ breast cancer is routinely treated with endocrine therapy.

Physicians had not offered a proposal of treatment strategy in 12 patients before ^{18}F-FES PET/CT scan. Diagnosis and management might be difficult due to insufficient checks to determine the characteristics of metastasis. Referring to the ^{18}F-FES PET/CT reports, 5 patients showed ^{18}F-FES positive lesion results and the particular ^{18}F-FES negative case mentioned above were considered for endocrine therapy and/or combined with other therapy, whereas the other 3 patients who showed consistently FES negative lesions were considered chemotherapy. For example, as shown as *Figure 1*. A 65-year-old woman who was diagnosed with ER-positive breast cancer in 2006 and papillary thyroid carcinoma in 2015 showed multiple metastases in bone. As we all know, bone metastasis could occur in both breast cancer and thyroid cancer (29). Treatment strategies of such two situations are definitely different. Endocrine therapy is suitable to the former and radioactive iodine (^{131}I) therapy is the common modality for treatment of the latter (30). Physician couldn't propose a clear treatment strategy for the patient until they read the ^{18}F-FES PET/CT report. The scan could provide evidence for whether the certain FES-positive breast cancer patient was suitable for endocrine

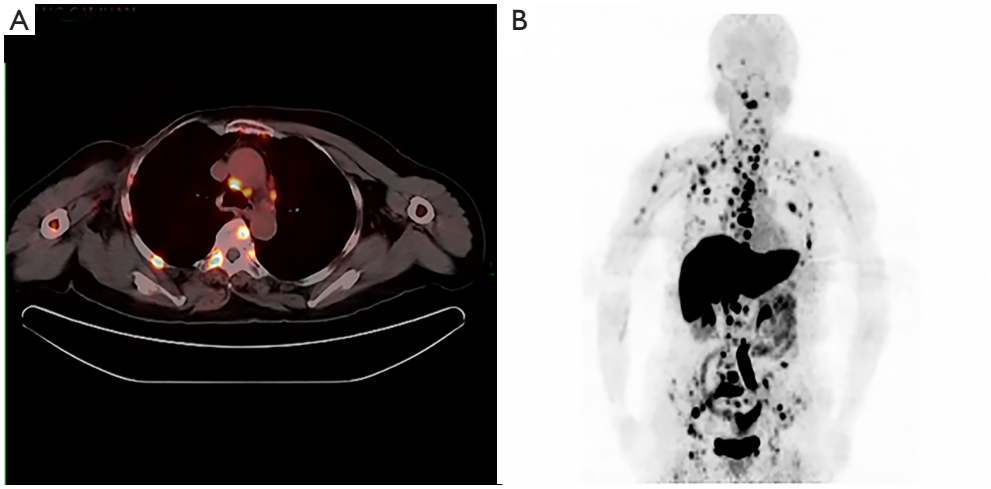

Figure 1 A 65-year-old woman with diagnosed ER-positive breast cancer in 2006 and papillary thyroid carcinoma in 2015. (A) Axial ^{18}F-FES PET/CT shows mediastinum lymph nodes and bone high uptake, considered to be ER-positive lesions. (B) ^{18}F-FES PET MIP demonstrates ^{18}F-FES avid focus in multiple body lesion. ER, estrogen receptor; ^{18}F-FES, ^{18}F-fluoroestradiol; PET, positron emission tomography; CT, computed tomography.

therapy (*Figure 1*). In fact, the therapy efficiency of the selected patient was evaluated SD after a regular endocrine therapy. The data suggested that ^{18}F-FES PET/CT scans could potentially help clinicians develop more efficient therapeutic strategies for stage IV patients diagnosed with ER-positive breast cancer and another primary cancer.

This study was partly limited by the relatively modest sample size because the population we studied had diagnosed double primary cancer, while other studies of ^{18}F-FES mainly focused on single ER-positive breast cancer. In addition, the major drawback of ^{18}F-FES is its high liver physiological uptake, making it unable to detect and diagnose liver lesions. Finally, the study lacks long-term follow-up outcomes for estimating the long-term efficacy of treatment strategy. We look forward to further randomized controlled trials on the significance and importance of ^{18}F-FES PET/CT in the diagnosis and treatment process of dual primary cancer in the future.

Conclusions

^{18}F-FES PET/CT scanning can be helpful in the diagnosis and treatment management of patients suffered from ER-positive breast cancer and another primary cancer, especially in detecting characteristics of metastasis. The proper application of ^{18}F-FES PET/CT could provide individualized management strategy for present and future clinical decision making in stage IV patients with dual primary cancers.

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Footnote

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